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**UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/794,851 02/04/97 BARANY

F 19603/461 (CR)

18N2/1216
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EXAMINER

RICIGLIANO, J

ART UNIT

PAPER NUMBER

1818

DATE MAILED:

12/16/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/794,851

Applicant(s)
Barany et al.

Examiner
Joseph W. Ricigliano Ph. D.

Group Art Unit
1818



☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle* 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

- ☒ Claim(s) 1-147 is/are pending in the application.
- Of the above, claim(s) 67-74 and 89-137 is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-66, 75-88, and 138-147 is/are rejected.
- ☒ Claim(s) 2, 5, 15, 17, 21, 23, 27, 29, 31, and 33 is/are objected to.
- ☐ Claims _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____.
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of References Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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DETAILED ACTION

1. This action is responsive to the amendments filed as listed below:
 - I, The preliminary amendment containing the raw sequence listing, electron sequence listing and detailing Seq I.D. enumeration in the specification has been entered.
 - ii, The supplemental information disclosure dated Sept. 29, 1997 has been entered.
 - iii, Request for a corrected filing receipt dated Oct. 8, 1997 has been entered.

Election/Restriction

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - I. Claims 1-88 and , 138-147 drawn to a method for identifying a plurality of nucleotide sequences employing immobilized oligonucleotides on a solid support, claims classified in class 435, subclass 6.
 - II. Claims 89-119, drawn to methods of forming arrays of nucleotides on a solid support, classified in class 536, subclass 25.31.
 - III. Claim 120-137, drawn to arrays of oligonucleotides on a solid support, classified in class 536, subclass 24.3.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and III are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the

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arrays of nucleotides on a solid support can be made by methods such as photolithography that are materially different than those described in process taught in invention II.

Inventions III and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product oligonucleotide arrays can be used for DNA sequencing on a solid phase as an alternative to the claimed use of capturing ligase chain reaction products.

Inventions I and II are related as separate methods. The methods have separate steps, require different reagents and have different end results. In the instant case Group II is directed to methods of forming arrays of nucleotides on a solid support, and Group I is directed to a method for identifying a plurality of nucleotide sequences employing immobilized oligonucleotides on a solid support. In addition, the method of Group I can employ immobilized arrays of nucleotides produced by methods other than the method of Group II.

If invention I is elected then an election species is required.

Claims 1 and 67 are generic to a plurality of disclosed patentably distinct species comprising

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I, claims 1-66, 75-88 and 138-147 directed to a method of using LDR (Ligase Detection Reaction) to detect DNA sequences providing a generic solid support having an array of capture oligo nucleotides.

ii, claims 67- 74 directed to a method of using LDR to detect DNA sequences providing specifically functionalized solid supports solid support having an array of capture oligo nucleotides.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Affirmation of this election must be made by applicant in responding to this Office action. Claim withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

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Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

During a telephone conversation with Michael Goldman on Dec. 3, 1997 a provisional election was made with traverse to prosecute the invention of the elected species, claims 1-66, 75-88 and 138-147. Affirmation of this election must be made by applicant in responding to this Office action. Claims 67-74 and 88-137 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-66, 75-88 and 138-147 are currently under consideration.

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Claim Rejections - 35 USC § 112

3. Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 44 recites the limitation "rate of formation". There is insufficient antecedent basis for this limitation in the claim. The specification does not teach or describe "rates of formation".

Claim 44 recites the limiting feature wherein the rate of formation of mismatched ligated product sequences is less than 0.005 of the rate of matched ligated product sequences. The specification fails to teach how to determine the rate of matched product and mismatched product sequences. It is unclear if the applicant is measuring the ratio of matched versus mismatched amplification products and dividing by the total amplification time or if a more dynamic methods such as direct fluorescence monitoring of amplification reaction products are intended. Last it is unclear how to interpret the "rate of formation" of matched and mismatched products when more than one of a plurality of target nucleotide sequences is being amplified and more than one mismatched product forms. Is the limiting rate of formation cumulative over all species of mismatched products versus all matched products, or does the rate refer to the each mismatched product independently?

4. Claims 12, 16, 18, 19, 20, 22, 26, 30, 34 and 81 are rejected under 35 U.S.C. 112, second

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paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 81 recites the limitation “each capture oligonucleotide differs from its adjacent capture oligonucleotide on the array by at least 25% of the nucleotides”. There are numerous methods by which sequence homology can be calculated and it is unclear by what means a 25% difference is to be determined.

Claims 12, 16, 18, 19, 20, 22, 26, 30 and recite the term “nearby”. The term “nearby” is indefinite as it is unclear what distances are encompassed by “nearby”, and thus does not clearly define the metes and bounds of the claimed subject matter.

5. Claims 2, 3, 4, 5, 15, 17, 21, 23, 25, 27, 29, 31 and 33 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. .

Each of these dependent claims recites the limitation: “wherein the oligonucleotide probes in a given set are suitable for ligation together at a ligation junction when hybridized adjacent to one another on a corresponding target nucleotide sequence due to perfect complementarity at the ligation junction...” This appears to be a failure to further limit the parent claims, since it is

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inherent in the ligase detection assay method (and hence the parent claims) that ligation occurs effectively only when there is perfect complementarity, or else the entire technique would be nonfunctional.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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7. Claims 1-5, 11-21 and 24-43, 45-66, 75-77, 79, 80, 83, 87, 88 and 138-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994).

Wiedmann et al., under the heading “Theory of LCR (Ligase Chain Reaction) and Similar Amplification Methods” teach “Ligase Detection Reaction (LDR) is similar to LCR” (page S51). Wiedmann et al. teach ligase detection assays employing primers that are complementary to the sequences to be detected and having a mismatch at the ligation junction for alternate alleles (see figure 2). Moreover, Wiedmann et al. teach “LDR may be used following a primary amplification (PCR, 3SR, QB-replicase, RT-PCR) and has the advantage of accurately quantitating the ratio of two alleles in a target sample. LDR coupled to PCR has promise in a multiplex format where several mutations are analyzed in a single amplification”(page S52). Wiedmann et al. also teaches the used of LCR include genetic diseases (including single base pair variations in alleles, sickle cell anemia and cystic fibrosis) bacteria and viruses (“Current Applications of LCR” starting on page 58 and Table 3). Wiedmann et al. also teaches the use of LCR and LDR in relation to oncogenes and cancer (Detection of Other Target Sequences, S61). Wiedmann et al. teach the use of numerous detection methods for ligase mediated nucleic acid amplification products including isotopic, affinity, luminescence and florescence techniques, and in addition, quantitation of products labeled with fluorophores and the use of multiple fluorophores simultaneously (see Detection Methods for LCR Products starting on page S57 and the last paragraph on page S60).

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Wiedmann et al. discusses the use of microtiter plate formats in the detection of ligase mediated amplification reaction products on page S58. Last, Wiedmann et al. also teach multiplex LCR employing as many as six primers simultaneously under the heading of Detection of Genetic Diseases on page S59).

While Wiedmann et al. teaches LDR and the closely related LCR technique are similar and that multiplexing can be employed with LCR reactions, Wiedmann et al. does not exemplify multiplexing or oligonucleotide probes as taught in the application or the use of thermostable ligases. Wiedmann et al. also fails to teach the use of nucleotide amplification reactions for forensic testing, evaluation of cancer and oncogenesis or environmental testing, the solid phase arrays or the techniques of detection and correlation.

Barany (1991a) teaches ligase detection assay as a sensitive assay for detecting and DNA sequences with high sensitivity in the presence of excess DNA (page 7, column 3 through page 8 column 1). Barany (1991a) specifically teaches "From a variety of exceedingly sensitive assays first described for ligase, it was readily apparent that this enzyme could serve as a reporter for the presence of two adjacent strands of DNA hybridized to a complementary strand." (column 3, page 7), which reads on the detection of any target strand provided the target strand sequence is known. Barany goes on to teach "Thermostable ligase discriminated single-base mismatches under both LDR (ligase detection reaction; using two adjacent probes) and LCR (ligase chain

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reaction; using two pairs of adjacent probes) conditions, with a signal to noise ratio ranging from 75 to greater than 500" (starting last paragraph of page 7). Indicating that even the subtlest single-base changes (found in some allelic variations) can be detected. Moreover, Barany (1991a) teaches radioactive, fluorescent, chemiluminescent fluorescent or enzymatic reporter groups are compatible with the closely related technique, ligase chain reaction (page 11, column 1) and several fluorescent probes (page 11, column 3). Barany also teaches that ligase chain reaction could detect a numerous mutations through a multiplexing format and that detection of multiple mutations "could allow for rapid testing of several hundred polymorphic disease mutations in a given gene (page 11, column 3). In table 1 (page 9) Barany teaches LCR reaction conditions where denaturation is carried out at 85 or 94 °C for 0.5 to 1 minute, using probes from 20-28 nucleotides long, wherein the target specific portion of the probes have a hybridization temperature in the range of 50-85 °C in one example and 62- 94 °C in two other examples, the cycle times range from 0.85 - 5 minutes and 20 to 40 cycles are used in the presence of carrier DNA. Barany et al. teach *T. aquaticus* and *T. thermophilus* ligases as thermostable ligases for use in LDR (page 7 columns 2 & 3). Last, Barany teaches that "Thermostable ligase will only ligate primers that are perfectly complementary to their target sequence and hybridize directly adjacent to each other..."(Figure 4 legend, page 11).

Zaun et al. teaches a multiplex method of amplifying and detecting target nucleic acids that including ligase chain reaction and variations on ligase chain reaction (column 1, lines 50-62). In Zaun et al.'s method, the primer pairs employed both have a target specific portion, in addition,

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one member of the pair has an addressable array specific portion (dansyl, adamantane, quinolin...), and the other has a reporter label (biotin). Zaun et al. also teaches detection of the amplification products based on visible and fluorescent labels (column 14, lines 37-44), quantitation of amplification products against a standard (column 35, lines 18- 46) and the use of solid supports for detecting amplification products made from a variety of materials including plastics, glass and synthetic polymers (see Detection Supports starting in column 9 at line 40). Moreover, the supports can be in a variety of shapes including sides and strips (films) and have capture sites (array) for the amplification products. Zaun et al teach a denaturation temperature range from about 80-100 C and (Column 18, line 62), LCR amplification using 10 - 70 cycles of amplification (Column 19, lines 40-43, with LCR reaction times in the range of two minutes and total reaction time is on the order of 80 minutes (see Examples 6, column 39. Zaun et al teach primer/probes from 15-100 base pairs (column 32, line 10-13). Zaun et al. also provide for the detection of visible and fluorescent labels employing a camera and computer (see Detection Systems, starting in column 14 at line 37)

Guo et al. teaches a multiplex method of amplifying and detecting target nucleic acids applied to genetic polymorphisms. In the method of Guo et al. the amplified nucleic acids are detected using fluorescently labeled tags on an immobilized oligonucleotide array (see abstract). Guo et al. also teaches the direct quantitation using fluorescence scanning and video imaging (see the example of Guo et al. on the simultaneous analysis of four tyrosinase single base mutations, pages 5460-5463). Last Guo teaches "One can readily envision the commercial production of

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DNA “chips” configured for tissue typing, cancer diagnosis, genetic identity testing, soil and environmental testing and many other applications”(page 6454).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Zaun et al., Guo et al. and Barany (1991a) with the ligase mediated amplification method of Wiedmann et al. because: Zaun et al had taught the use of a multiplex DNA ligase mediated nucleotide amplification method using primers having a target specific portion and a reporter label or an array specific portion, providing detection and quantitation on solid supports having capture agents arranged in arrays for ligase mediated amplification products; Guo et al. taught a multiplex method of amplifying and detecting target nucleic acids applied to genetic polymorphisms employing multiple fluorescent tagged primers and an immobilized oligonucleotide array for detection and direct quantitation of nucleotide amplification products; Guo et al. also recognize the commercial potential of immobilized nucleotide arrays for detecting specific nucleotide sequences; Barany (1991a) taught multiplexing of the ligase amplification reactions, DNA ligase mediated reaction conditions and acceptable target sequences, detection of ligase mediated amplification products, and the thermophilic ligases employed in ligase mediated amplification reactions and Wiedmann et al. taught that LDR and LCR are similar reactions, additionally Wiedmann et al. taught diverse detection techniques, some detection formats and prior amplification of target sequences, the use of these reactions for the detection of numerous DNA targets including pathogenic agents, allelic variations, single base pair mismatches and oncogenes.

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One of ordinary skill in the art would have been motivated to combine these teachings in order to effectively identify or candidate multiple target nucleotide sequences present in a sample with high sensitivity and low background, thereby permitting them to determine quantity and diversity of genetic alterations that are known or to detect nucleotide sequences known to be associated with pathogenic organisms, an abnormal state or biological phenotype simultaneously. Furthermore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to supply the materials required for the method as a kit because Guo et al. had taught the immobilized arrays of nucleotides for a variety of test could be envisioned in commercial production. One of ordinary skill in the art would have been motivated to construct a kit in order to provide researchers or laboratory/field analysts with a quality controlled group of materials and standards which would make testing more reproducible, affordable and easier to conduct.

8. Claims 6-10, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77, 79, 80, 83, 87, 88 and 138-147 *supra* in further view Telenti et al.

See the teaching Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77, 79, 80, 83, 87, 88 and 138-147 *supra*

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The references as combined above fail to teach the quantitation of nucleotide amplification reaction products by providing a known amount of a nucleotide sequence as an internal standard.

Telenti et al.(1992) teach that PCR, another nucleotide amplification reaction, can be quantitated by providing a known amount of an internal standard sequence (abstract, page 259).

It would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art to combine the use of an internal standard as a quantitation method as taught by Telenti et al. for the quantitation of PCR products with the ligase amplification reaction as taught by the references as combined *supra*, because Telenti et al. taught the use of internal standards (or “competitive strands” as they are sometimes called by others) for quantitation of nucleic acid amplification products. One of ordinary skill in the art would have been motivated to do so to obtain a direct assessment of the amount of target present in their assay samples and to be able to normalize the sample results for quantitative comparison.

9. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 *supra*, in further view of Barany (1991b).

See the teaching Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994)as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 *supra*.

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The references a combined above fail to teach determination of the rate of formation of mismatched and matched LDR products.

Barany (1991b) teaches the determination of LDR reaction products in the presence of matched and mismatched bases (page 191, Table 1), wherein the mismatched/complementary products ratio is less than 0.4%.; that is to say the formation of mismatched product occurs at a rate < 0.004 that of matched or complementary product.

It would have been prima facie obvious at the time the invention was made to one of ordinary skill in the art to employ LDR reaction conditions that gave a rate of mismatched product formation less than 0.005 of the rate of matched product formation in the LDR detection method as taught by the combined references supra, because Barany had previously had taught that LDR reactions could achieve rates of mismatched product formation less than 0.004 of the rate of matched product formation. One of ordinary skill in the art would have been motivated to do so in order to obtain an assay which was highly specific for the a target nucleotide sequence.

10. Claims 78, 82, 84-86 are rejected under 35 U.S.C. 103(a) as being unpatentable Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 under 35 U.S.C. 103(a) supra in further view of Sambrook et al.

See the teachings Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 under 35 U.S.C. 103(a) supra.

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The references as combined above fail to teach methods of hybridization the stripping of blots for reuse or the use of exonucleases.

Sambrook et al. teach hybridization of Southern-blotting using oligonucleotide probes and the use of nucleotides (sheared and denatured salmon sperm DNA) between target oligonucleotides to which probes do not bind with specificity (pages 9.47-9.55). Sambrook also teaches the cleaning (or stripping) of Southern blots (page (9.58) and the use of exonucleases (see page 5.78-5.79 and 5.84-5.85).

It would have been prima facie obvious at the time the invention was made to one of ordinary skill in the art to employ: the conditions for hybridizing oligonucleotide probes to immobilized nucleotides (Southern-blotting), barrier oligonucleotides, exonucleases to destroy nucleotides and the stripping of blots as taught by Sambrook et al. with the LDR methods as taught by the references combined *supra*, because Sambrook et al. had taught Southern blot techniques and the use of exonucleases to destroy DNA. One of ordinary skill in the art would have been motivated to use these methodologies in order to obtain clear specific hybridization of nucleotide probes to immobilized target nucleotides with a low background and to be able to reuse the immobilized array of nucleotides which can be difficult, time consuming and expensive to prepare.

11. No claims are allowed.

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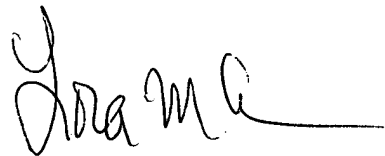
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano whose telephone number is (703) 308-9346. The examiner can normally be reached on Monday through Friday from 8AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lora Green, can be reached on (703) 308-3999.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.


JWR

December 10, 1997



LORA M. GREEN
PRIMARY EXAMINER
GROUP 1800